REMARKS

This Amendment is being submitted in response to the Office Action mailed on March 6, 2006. Reconsideration of the above-identified application in view of the foregoing amendments and following arguments is respectfully requested.

Double Patenting

The Examiner provisionally rejected claims 1-9 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending U.S. Application No. 10/611,044. Applicants respectfully traverse this rejection.

While not agreeing with the rejection, in order to expedite prosecution, Applicants herewith enclose an executed a terminal disclaimer in compliance with 37 CFR 1.321(c). Also enclosed herewith is a terminal disclaimer fee in the amount of $130.00.

Therefore, in view of the submission of the enclosed terminal disclaimer, Applicants submit that this rejection is now moot and should be withdrawn.

Rejection of Claims 1, 2, and 5 Under 35 U.S.C. §102(a) and §102(e)

Claims 1, 2, and 5 are rejected under 35 U.S.C. §102(a) and §102(e) as being anticipated by WO 02/45692 (hereinafter "WO '692"). The Examiner asserts that WO '692 discloses compositions comprising acid labile drugs, specifically proton pump inhibitors in a suspension to be administered to a patient in need thereof. The Examiner further asserts that WO '692 teaches coating these oral dosage forms of acid labile active ingredients with an enteric coating (See page 4 of the Office Action). Applicants respectfully traverse this rejection.

Applicants respectfully submit that WO'692 does not disclose or suggest

Applicant's invention. In particular, while, the "Background" section of WO '692 discloses that there are many problems associated with the prior art coatings of acid labile drugs, the proposed solution to those problems is very different than the approach taken by Applicants. The compositions of WO '692 comprise an aqueous base, an excipient, a thickener and a matrix composed of at least one paraffin (See, WO '692, page 3, first full paragraph). WO '692 specifically discloses that its compositions do not comprise enteric coatings. Specifically, on the bottom of page 2, last paragraph through lines 1-3 of page 3, WO '692 states, "It is an object of the present invention to provide a juice (hereinafter also referred to as suspension) for the oral administration of acid-labile active ingredients which can be produced without great technical complexity, which is stable and not sensitive to moisture and displays good controllability of active ingredient delivery. It ought also be possible to produce the suspension ready for use. Another object of the invention is also to provide a suspension for the oral administration of acid-labile active ingredients, where it is <u>unnecessary to protect the acid-labile active ingredient by an enteric coating</u>" (emphasis added). In contrast, the claimed invention requires that the micro-granules be coated with an enteric coating.

According to the *Manuel of Patenting Examining Procedure* Section 2131 (8^{th} Edition August 2005 Revision), a claim is anticipated only if each and every element set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Therefore, because WO '692 does not teach each and every element of the claimed invention, this reference does not anticipate claims 1, 2 and 5. Thereupon, these rejections should be withdrawn.

<u>Rejection of Claims 1-11 Under 35 U.S.C. §103 (a)</u>

Claims 1-9 are rejected under 35 U.S.C. §103(a) as being obvious over WO 02/45692 (WO '692) and over WO 94/25070 (the '070 application) in view of WO 02/45692. Applicants respectfully traverse the rejection.

a) Rejection over WO '692

The Examiner states that WO '692 discloses that it is known to coat acid labile drugs with enteric coatings. WO '692 merely discloses that this is generally known in the "Background" section, while going on to explain that there are many problems associated with prior art enteric coatings of acid labile drugs. The actual compositions disclosed in WO '692 do not contain an enteric coating, as WO '692 was seeking to avoid the problems associated with such coatings by using a different formulation. (See the Applicants' discussion of the §§102(a) and (e) rejections above).

The Examiner cites Example 6 and Example C of WO '692 and argues that "it would have been obvious to one of ordinary skill in the art to provide a suspension with the specific pH requirements such that the enterically coated microgranules would not dissolve in the liquid vehicle, but would form a suspension. As Example C discloses that in the suspension a desirable swelling is achieved this would leave one of ordinary skill in the art to expect that the solution is in a pH range sufficiently low to prevent the degradation of the enterically coated microgranules." (See, the Office Action, page 6).

Applicants respectfully traverse this rejection. As Applicants explained above, WO '692 discloses acid labile drug compositions in a paraffin matrix, not with an enteric coating. These compositions are very different from the compositions claimed by Applicants. Specifically, Example 6 of WO '692 discloses how to prepare a matrix composition. Example C discloses how to make a suspension of the matrix composition prepared according to Example 6. Since the matrix composition of Example 6 is significantly different from the compositions claimed in the instant invention (namely, the compositions of WO '692 use a paraffin wax rather than an enteric coating), a suspension of Example C is also very different from Applicants' presently claimed compositions.

More specifically, as discussed in the *Handbook of Pharmaceutical Excipients,* 4th edition, Eds. Rowe, R.C., Sheskey, PJ and Weller, PJ (Pharmaceutical Press), paraffins are purified mixtures of solid saturated hydrocarbons that are obtained from petroleum or shale oil. Paraffins are practically insoluble in water and are stored at temperatures of not more than 40°C. Functionally, paraffins are used as a base for ointments and as stiffening agents. Paraffins are included in the FDA's Inactive Ingredients Guide and are used in oral capsules and tablets and topical emulsions and ointments.

The compositions of the present invention, the acid-labile drug is coated with an enteric coating. Thereupon, the release of the acid-labile drug is delayed until the composition reaches the small intestine. In contrast, Additionally, the compositions of WO '692 will be subjected to acid degradation and drug release in the stomach. Moreover, the compositions of the present invention are liquid formulations that can be administered via feeding tubes to patients in need of treatment thereof. As mentioned above, paraffins are temperature sensitive and are stored at temperatures of not more than 40°C. In fact, because of this temperature sensitivity, the compositions described in WO '692 would be very difficult to administer via a feeding tube as these compositions could potentially clog and block the tube, thus leading to obvious safety concerns for the patient. Moreover, the performance of compositions containing paraffins would be temperature dependent. Specifically, if the formulation of such compositions are varied by a few degrees, the release of the drug as well as the protection of the composition from acid degradation in the stomach, will be greatly varied. Thus, the pharmacokinetic profiles of the composition of described in WO '692 will be very different than the pharmacokinetic profiles of the compositions of the present invention.

The compositions of the present invention provide a number of advantages. Specifically, these compositions can be titrated to provide varying doses (such as 2 mg, 5 mg, 8 mg, etc.) Additionally, uniform dosing can be

provided to a patient. Titration of the compositions containing the paraffin matrix described in WO '692 is not possible. Moreover, given the nature of these compositions, it would be difficult to provide uniform dosing as with the compositions of the present invention. Therefore, in summary, compositions containing paraffins and compositions containing enteric coatings are very different compositions.

Applicants submit that it would not be obvious to one skilled in the art to replace the matrix disclosed in Examples 6 and C with an enteric coating. Similarly, the claimed kits of the present invention are also not obvious over the compositions disclosed in WO '692 since any kit comprising the components of WO '692 would comprise a matrix containing at least a paraffin wax and would not comprise an enteric coating. In fact, WO '692 actually teaches away from the use of enteric coatings because of the problems associated with these coatings and suggests compositions that do not contain enteric coatings.

Therefore, Applicants submit that claims 1-9 are not obvious under 35 U.S.C. Section 103(a) over the compositions disclosed in WO '692.

b) <u>Rejection over WO 94/25070 in view of WO 02/45692</u>

The Examiner states that WO '070 teaches a pharmaceutical composition for oral administration to animals comprising a proton pump inhibitor in the form of beads that are enterically coated and incorporated with a pH buffer into water or a water solution (See, Office Action, page 7). The Examiner further states that the pH buffer is used to decrease the pH of the solution to 5.5 or below and that this reference also teaches making a kit comprising the dry enteric coating beads. The Examiner admits that WO '070 does not teach making microparticles of the proton pump inhibitor or the viscosity requirement. However, the Examiner claims that WO '692 cures this deficiency. *Id.* According to the Examiner, "it would have been obvious to one of ordinary skill in the art to make microparticles because WO '692 teaches that is (sic) well known in the art to do so. One of

ordinary skill in the art would have been motivated to make microparticles because microparticles make a more uniform suspension. One of ordinary skill in the art would have been motivated to make a solution with a viscosity that is suitable to form a suspension, and would look thus to WO '692 that teaches that by adding thickening agents the desired viscosity can be achieved" (See, Office Action, page 8).

Applicants respectfully disagree. First, WO '070 does not disclose or suggest compositions comprising a liquid vehicle as recited in the claims of the instant application. Rather, WO '070 discloses paste-like gel compositions comprising proton pump inhibitors (See, WO '070, page 3). By definition, paste-like gel compositions are different from liquid compositions. Specifically, as shown discussed in *Remington, The Science and Practice of Pharmacy 21st Edition* (hereinafter "Remington"), which is attached herewith, the USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application. As discussed further in Remington, "[P]astes adhere reasonably well to the skin and are poorly occlusive. For this reason, they are suited for application on or around moist lesions. The heavy consistency of pastes imply a degree of protection and may, in some instances, make the use of bandages unnecessary." With respect to gels, as discussed in Remington, gels are semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules in the dispersed phase (See Remington, page 770). As further discussed by Remington and pursuant to the USP, gels are used to administer drugs topically or into body cavities. *Id.* Additionally, as discussed above, the compositions of the present invention provide a number of advantages. Specifically, these compositions can be titrated to provide varying doses and uniform dosing can be provided to a patient in need of treatment. Titration of the compositions containing paste-like gel compositions as described in WO '070 is not possible. Moreover, given the nature of these compositions it would be difficult to provide uniform dosing. Thereupon, there is no suggestion

or motivation in either WO '652 or WO '070 to modify the paste-like gel composition of WO '070 to a liquid form.

WO '692 does not cure the deficiencies of WO '070. Contrary to the Examiner's position, WO '692 does not teach coating the compositions with enteric coatings. As explained above, WO '692 only discloses that some prior art compositions utilized enteric coatings. It does not disclose or suggest that the prior art compositions comprised microgranules or that prior art compositions comprised a liquid vehicle having a pH less than 6.0. On the contrary, WO '692 teaches away from Applicants' invention by pointing out the various problems associated with the prior art compositions, such as dissolution of the coating from the inside, thus requiring a sealing intermediate layer (See, WO '692, page 1). As discussed several times herein, WO '692 teaches way from compositions containing enteric coatings. Moreover, as also discussed previously herein, the compositions disclosed in WO '692 require the use of a paraffin matrix. The paraffin matrix of the compositions in WO '692 are very different compositions than the compositions of the present invention which use an enteric coating.

Therefore, while WO '692 discloses that some prior art acid labile compositions comprise enteric coatings, it does not suggest or motivate a person skilled in the art to modify the compositions of WO '070 to arrive at the Applicants' claimed compositions, namely, compositions comprising microgranules with enteric coatings, a liquid suspension vehicle having a pH less than 6.0 and having a viscosity sufficient to suspend the microgranules. To the contrary, WO '692 actually teaches away from such a modification.

In summary, the compositions of WO '692 and WO '070 are significantly different from Applicants' claimed compositions. WO '070 discloses paste-like gel compositions that do not comprise microgranules. WO '692 discloses suspensions, which while seeking to avoid the problems with enteric coatings, do require a matrix that comprises at least a paraffin. Thereupon, there is nothing

in WO ‘692 and WO ‘070, either individually, or collectively, which discloses or suggests the claimed invention. Therefore, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and that the rejection of claims 1-9 as being obvious over WO ‘070 in view of WO ‘692 should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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EXTEMPORANEOUS PREPARATIONS FROM TABLETS AND CAPSULES

Occasionally, it is necessary to prepare a liquid formulation of a drug to meet certain patient requirements. Consequently, patients who are unable to swallow solid medications, require a different route of administration or different dosing strength present a special need. Thus, the pharmacist may have to extemporaneously compound a liquid product. If the pure drug is available, it should be used to prepare the liquid dosage form. If it is necessary to prepare a liquid dosage form from tablets or capsules, a suspension is formed if either the drug or one of the excipients in the tablets or capsules is insoluble. Insoluble excipients in these dosage forms include disintegrants, lubricants, glidants, colors, diluents, and coatings. Consequently, although the drug may be soluble in water, many excipients are not. It is preferable to use the contents of capsules, or tablets that are not coated. If coated, tablets with a water-soluble coat are preferred to those with functional enteric coatings and the like. In any case, the contents of the capsules or the tablets should be ground finely with a ceramic mortar and pestle and then wetted using alcohol or glycerin.

Preservatives may be included in the liquid formulation to enhance the stability. However, preservatives have been found to cause serious adverse effects in infants. Benzyl alcohol should be omitted from neonatal formulations because it can cause a gasping syndrome characterized by a deterioration of multiple organ systems and eventually death. Propylene glycol has also been implicated to cause seizures and stupor in some preterm infants. Thus, formulations for neonates should be purposely kept simple, and not compounded to supply more than just a few days of medicine

Finally, it may be desirable to use a hand homogenizer to prepare a more suitable product. Some drugs that have been formulated in this manner include clonidine hydrochloride and simple syrup,[92] cefuroxime axetil in an orange syrup vehicle,[93] and famotidine in cherry syrup.[94] Many other examples may be found in current hospital and community pharmacy journals such as the *American Journal of Hospital Pharmacy, Canadian Journal of Hospital Pharmacy, U.S. Pharmacist, International Journal of Pharmaceutical Compounding,* and *Drug Development and Industrial Pharmacy.* Frequently, stability data and, occasionally, bioavailability and/or taste data are provided.

To minimize stability problems of the extemporaneously prepared product, it should be placed in air-tight, light-resistant containers and stored in the refrigerator by the patient. Because it is a suspension, the patient should be counseled to shake it well prior to use and to be aware of any change that might indicate a stability problem with the formulation.

Tortorici reports an example of an extemporaneous suspension of cimetidine tablets that retained its potency at 40° over 14 days.[95] Twenty-four, 300 mg cimetidine tablets are compounded with 10 mL of glycerin and 120 mL of simple syrup. The tablets are triturated to a fine powder using a mortar, the mixture is levigated with the glycerin, and the simple syrup added. The suspension is mixed well, placed in a blender until smooth, and then refrigerated.

SUSTAINED RELEASE SUSPENSIONS

Sustained release suspensions represent a very specialized class of preparation. Sustained release, oral suspensions with morphine,[96] nonsteroidal anti-inflammatory agents,[97] and other drugs[98] have been described in the literature. However, limited commercial success has been achieved due to the difficulty in maintaining the stability. Formulation research for sustained release suspensions has focused on the similar technologies used in preparing sustained release tablets and capsules. *Celltech* licenses the Tussionex Pennkinetic system, which uses a combination of ion exchange resin and particle coating.[99] This novel system exploits the likelihood of complexation between ionic drugs and ion-exchange resins, which are then coated with ethyl cellulose. When administered orally, the coated particles with encapsulated drug adsorbed onto the resin are slowly released by an ion exchange process.

Durect markets the SABER system for sustained release suspension applications. SABER uses a non-polymeric, non-water-soluble high-viscosity liquid carrier material (>5,000 cPa at 37°C), such as sucrose acetate isobutyrate (SAIB), to provide controlled release of active ingredients.[100] The drug is mixed with a small amount of a pharmaceutically acceptable solvent to form a low viscosity solution or suspension, which is then mixed with the high viscosity carrier. The resulting suspension can be administered via injection, orally, or as an aerosol, forming an adhesive, biodegradable depot upon contact with tissues. After administration of the SABER formulation, the solvent diffuses away, leaving a viscous, adhesive matrix of the three components—SAIB, drug, and any additives. The release rate can be easily modified by the ratio of non-polymeric, non-water-soluble high-viscosity liquid carrier material present in the formulation. Extended systemic and local delivery for durations of 1 day to 3 months from a single injection has been demonstrated.

GELS AND MAGMAS

Gels are defined by the USP as:

> "...semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma. Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation.
>
> Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules or from natural gums. The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.
>
> Gels can be used to administer drugs topically or into body cavities."

Gels are also defined as semi-rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules in the dispersed phase. Physical and / or chemical cross-linking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semisolid state.

Some gel systems are clear and others are turbid, since the ingredients involved may not be completely soluble or insoluble, or they may form aggregates, which disperse light. The concentration of the gelling agents is generally less than 10%, and usually in 0.5 to 2.0% range. Gels in which the macromolecules are distributed throughout the liquid in such a manner that no apparent boundaries exist between them and the liquid are called single-phase gels. In instances in which the gel mass consists of floccules of small distinct particles, the gel is classified as a two-phase system and frequently called a magma or a milk. Gels and magmas are considered colloidal dispersions since they each contain particles of colloidal dimension

Different types of colloidal dispersions have been given specific names. For instance, *sol* is a general term designating a dispersion of a solid substance in a liquid, a solid, or a gaseous

dispersion medium. However, more often than not it is used to describe the solid liquid dispersion system. A prefix such as hydro- for water (*hydrosol*) or alco- for alcohol (*alcosol*) is used to specify the medium. Similarly, *aerosol* has similarly been developed to indicate a dispersion of a solid or a liquid in a gaseous phase.

The generally accepted size range for a substance "colloidal" is when particles fall between 1 nm and 0.5 μm. One difference between colloidal dispersions and true solutions is the larger particle size of the dispersed phase in colloidal systems. The optical properties of the two systems are also different. True solutions do not scatter light and therefore appear clear, but colloidal dispersions contain discrete particles scatter light.

Gelling Agents

Several compendial materials function as gelling agents, including acacia, alginic acid, bentonite, carbomer, carboxymethylcellulose sodium, cetostearyl alcohol, colloidal silicon dioxide, ethylcellulose, gelatin, guar gum, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminum silicate, maltodextrin, methylcellulose, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch, tragacanth, and xanthan gum.

Alginic acid is refined from seaweed. It is a tasteless, practically odorless, white to off-white colored, fibrous powder. It is used in concentrations between 1% and 5% as a thickening agent, and swells in water to about 200 times its own weight without dissolving. Alginic acid can be cross-linked by addition of calcium salts, resulting in substantially higher viscosity. Sodium alginate produces a gel at concentrations up to 10%. Aqueous preparations are most stable between pH values of 4–10; below pH 3, alginic acid is precipitated. Sodium alginate gels for external use should be preserved.

Carbomer resins are high molecular weight, acrylic acid-based polymers. The pH of 0.5% and 1.0% aqueous dispersions are 2.7–3.5 and 2.5–3.0, respectively. There are many carbomer resins, with viscosity ranges available from 0 to 80,000 cPs., depending upon the pH to which it is neutralized. In addition to thickening, suspending, and emulsifying in both oral and topical formulations, carbomers are also used to provide sustained release properties in both the stomach and intestinal tract for commercial products. Alcohol is often added to carbomer gels to decrease their viscosity. Carbomer gel viscosity is also dependent upon the presence of electrolytes and the pH. Generally, a rubbery mass forms if greater than 3% electrolytes are added. Carbomer preparations are primarily used in aqueous systems, although other liquids can be used. In water, a single particle of carbomer will wet very rapidly but, like many other powders, carbomer polymers tend to form clumps of particles when haphazardly dispersed in polar solvents. Rapid dispersion of carbomers can be achieved by adding the powder very slowly into the vortex of the liquid that is very rapidly stirred. A neutralizer is added to thicken the gel after the carbomer is dispersed. Sodium hydroxide or potassium hydroxide can be used in carbomer dispersions containing less than 20% alcohol. Triethanolamine will neutralize carbomer resins containing up to 50% ethanol.

Carboxymethylcellulose (CMC) produces gels when used in concentrations of 4% to 6% of the medium viscosity grade. Glycerin may be added to prevent drying. Precipitation will occur at pH values less than 2, it is most stable at pH levels between 2 and 10, with maximum stability at pH 7 to 9. It is incompatible with ethanol. Sodium carboxymethylcellulose (NaCMC) is soluble in water and should be dispersed with high shear in cold water before the particles hydrate and swell. Once the powder is well dispersed, the solution is heated with moderate shear to about 60°C for fastest dissolution. These colloidal dispersions are sensitive to pH and the viscosity of the product decreases below pH 5 or above pH 10.

Tragacanth gum has been used to prepare gels that are stable at a pH range of 4–8. These gels must be preserved or sterilized by autoclaving. Tragacanth often lumps when added to water, thus, aqueous dispersions are prepared by adding the powder to rapidly mixed water. Also, lumps are also prevented by wetting the gum with ethanol, glycerin, or propylene glycol.

Colloidal silicon dioxide can be used to prepare transparent gels when used with other ingredients of similar refractive index. Colloidal silicon dioxide adsorbs large quantities of water without liquefying, and its viscosity is largely independent of temperature. Changes in pH affect the viscosity: it is most effective at pH values up to about 7.5. Colloidal silicon dioxide (fumed silica) will form a hydrophobic gel when combined with 1-dodecanol and n-dodecane. These are prepared by adding the silica to the vehicle and sonicating for about 1 minute to obtain a uniform dispersion, sealing, and storing at about 40°C overnight.

Gelatin gels are prepared by dispersing gelatin in hot water followed by cooling. Alternatively, gelatin can be wetted with an organic liquid such as ethyl alcohol or propylene glycol followed by the addition of the hot water and cooling. Magnesium aluminum silicate forms thixtropic gels at concentrations of about 10%. The material is inert and has few incompatibilities but is best used above pH 3.5. It may bind to some drugs and limit their availability.

Methylcellulose forms gels at concentrations up to about 5%. Since methylcellulose hydrates slowly in hot water, the powder is dispersed with high shear at 80–90°C in a portion of water. Once the powder is finely dispersed, the remaining water is added with moderate stirring. Alcohol or propylene glycol is often used to help wet the powders. High electrolyte concentrations will salt out the polymer, ultimately precipitating the polymer.

Poloxamer gels are made from selected forms of polyoxyethylene-polyoxypropylene copolymers in concentrations ranging from 15% to 50%. Poloxamers are white, waxy, free-flowing granules that are practically odorless and tasteless. Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Polyvinyl alcohol (PVA) is used at concentrations of about 2.5% in the preparation of various jellies, which dry rapidly when applied to the skin. Borax is a often used to gel PVA solutions. For best results, disperse PVA in cold water, followed by hot water. It is less soluble in the cold water.

Povidone, in the higher molecular weight forms, can be used to prepare gels in concentrations up to about 10%. It has the advantage of being compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It has also been used to increase the solubility of a number of poorly soluble drugs.

Two-Phase Gels

Two-phase gels containing bentonite may be used as a base for topical preparations such as plaster and ointment. Aluminum Hydroxide Gel, USP is an example of a two-phase gel. The USP states that "Aluminum Hydroxide Gel is a suspension of amorphous aluminum hydroxide in which there is a partial substitution of carbonate for hydroxide." The gel is usually prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate, or bicarbonate. The reactions that occur during the preparation are

$$3CO_3^{2-} + 3H_2O \rightarrow 3HCO_3^- + 3OH^-$$

$$[Al(H_2O)_6]^{3+} + 3OH^- \rightarrow [Al(H_2O)_3(OH)_3] + 3H_2O$$

$$2HCO_3^- \rightarrow CO_3^{2-} + H_2O + CO_2$$

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used, and the conditions of aging of the precipitated gel.

Table 44-5. Density Factors for Cocoa Butter Suppositories

MEDICATION	FACTOR	MEDICATION	FACTOR
Alum	1.7	Menthol	0.7
Aminophylline	1.1	Morphine HCl	1.6
Aminopyrine	1.3	Opium	1.4
Aspirin	1.3	Paraffin	1.0
Barbital	1.2	Peruvian balsam[a]	1.1
Belladonna extract	1.3	Phenobarbital	1.2
Benzoic acid	1.5	Phenol[a]	0.9
Bismuth carbonate	4.5	Potassium bromide	2.2
Bismuth salicylate	4.5	Potassium iodide	4.5
Bismuth subgallate	2.7	Procaine	1.2
Bismuth subnitrate	6.0	Quinine HCl	1.2
Boric acid	1.5	Resorcinol	1.4
Castor oil	1.0	Salicylic acid	1.3
Chloral hydrate	1.3	Sodium bromide	2.3
Cocaine HCl	1.3	Spermaceti	1.0
Digitalis leaf	1.6	Sulfathiazole	1.6
Gallic acid	2.0	Tannic acid	1.6
Glycerin	1.6	White wax	1.0
Ichthammol	1.1	Witch hazel fluidextract	1.1
Iodoform	4.0	Zinc oxide	4.0
		Zinc sulfate	2.8

[a] Density adjusted taking into account white wax in mass.
Data from Davis H. *Bentley's Text-Book of Pharmaceutics,* 7th ed. London: Bailliere, Tindall & Cox, 1961 and Buchi J. *Pharma Acta Helv* 1940;20:403.

tor, or the density compared with cocoa butter, of many substances used in suppositories.

It always is possible to determine the density of a medicinal substance relative to cocoa butter, if the density factor is not available, by mixing the amount of drug for one or more suppositories with a small quantity of cocoa butter, pouring the mixture into a suppository mold and carefully filling the mold with additional melted cocoa butter. The cooled suppositories are weighed, providing data from which a working formula can be calculated as well as the density factor itself.

When using suppository bases other than cocoa butter, such as a polyethylene glycol base, it is necessary to know either the density of the drug relative to the new base or the densities of both the drug and the new base relative to cocoa butter. The density factor for a base other than cocoa butter is simply the ratio of the blank weights of the base and cocoa butter.

For instance, if a suppository is to contain 0.1 g tannic acid in a polyethylene glycol base, then 0.1 g $\div$ 1.6 x 1.25, or 0.078 g, polyethylene glycol base should be replaced by 0.1 g drug (the polyethylene glycol base is assumed to have a density factor of 1.25). If the blank weight is 1.75 g for the polyethylene glycol base, then 1.75 g - 0.078 g, or 1.672 g, of base is required per suppository. The final weight will be 1.672 g base + 0.1 g drug, or 1.772 g.

When the dosage and mold calibration are complete the drug-base mass should be prepared using minimum heat. A water bath or water jacket usually is used. The melted mass should be stirred constantly but slowly to avoid air entrapment. The mass should be poured into the mold openings slowly. Prelubrication of the mold will depend on the vehicle. Mineral oil is a good lubricant for cocoa butter suppositories. Molds should be dry for polyethylene glycol suppositories.

After pouring into tightly clamped molds the suppositories and mold are allowed to cool thoroughly using refrigeration on a small scale or refrigerated air on a larger scale. After thorough chilling any excess suppository mass should be removed from the mold by scraping, the mold opened, and the suppositories removed. It is important to allow cooling time adequate for suppository contraction. This aids in removal and minimizes splitting of the finished suppository.

PACKAGING AND STORAGE—Suppositories often are packaged in partitioned boxes that hold the suppositories upright. Glycerin and glycerinated gelatin suppositories often are packaged in tightly closed screwcapped glass containers. Though many commercial suppositories are wrapped individually in aluminum foil or PVC-polyethylene, strip-packaging is commonplace.

Alternatively, suppositories may be molded directly into their primary packaging. In this operation the form into which the suppository mass flows consists of a series of individual molds formed from plastic or foil. After the suppository is poured and cooled, the excess is trimmed off, and the units are sealed and cut into 3s or 6s as desired. Cooling and final cartoning then can be carried out.

Suppositories with low-melting ingredients are best stored in a cool place. Theobroma oil suppositories, in particular, should be refrigerated.

OTHER MEDICATED APPLICATIONS

Poultices (Cataplasms)

Poultices, or cataplasms, represent one of the most ancient classes of pharmaceutical preparations. A poultice is a soft, moist mass of meal, herbs, seed, etc, usually applied hot in cloth. The consistency is gruel-like, which is probably the origin of the word poultice.

Cataplasms were intended to localize infectious material in the body or to act as counterirritants. The materials tended to be absorptive, which together with heat accounts for their popular use. None is now official in the USP. The last official product was Kaolin Poultice NF IX.

Pastes

The USP defines pastes as semisolid dosage forms that contain one or more drug substances intended for topical application. Pastes are divided into fatty pastes (eg, Zinc Oxide Paste) and those made from a single-phase aqueous gel (eg, Carboxymethylcellulose Sodium Paste). Another official paste is Triamcinolone Acetonide Dental Paste.

The term *paste* is applied to ointments in which large amounts of solids have been incorporated (eg, Zinc Oxide Paste). In the past, pastes have been defined as concentrates of absorptive powders dispersed (usually) in petrolatum or hydrophilic petrolatum. These fatty pastes are stiff to the point of dryness and are reasonably absorptive considering they have a petrolatum base. Pastes often are used in the treatment of oozing lesions, where they act to absorb serous secretions. Pastes also are used to limit the area of treatment by acting both as an absorbent and a physical dam.

Pastes adhere reasonably well to the skin and are poorly occlusive. For this reason, they are suited for application on and around moist lesions. The heavy consistency of pastes imparts a degree of protection and may, in some instances, make the use of bandages unnecessary. Pastes are less macerating than ointments.

Because of their physical properties pastes may be removed from the skin by the use of mineral oil or a vegetable oil. This is particularly necessary when the underlying or surrounding skin is traumatized easily.

Powders

Powders for external use usually are described as dusting powders. Such powders should have a particle size of not more than 150 μm (ie, less than 100-mesh) to avoid any sensation of grittiness, which could irritate traumatized skin. Dusting powders usually contain starch, talc, and zinc stearate. Absorbable Dusting Powder USP is composed of starch treated with epichlorohydrin, with not more than 2.0% magnesium oxide added to maintain the modified starch in impalpable powder form; as it is intended for use as a lubricant for surgical gloves it should be sterilized (by autoclaving) and packaged in sealed paper packets.